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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/393,590	MOYER ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *29-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *41505*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendments

1) Acknowledgment is made of Applicants' amendments/responses filed 12/01/04, 03/09/05 and 04/15/05 in response to the non-final Office Action mailed 06/01/04.

Status of Claims

2) Claims 1-4, 9-13, 16-19 and 22-26 have been amended via the amendment filed 12/01/04.

Claims 1-4, 9-13, 16-19 and 22-26 have been amended via the amendment filed 03/09/05.

Claims 1-53 are pending.

Claims 1-28 are under examination.

Information Disclosure Statement

3) Acknowledgment is made of Applicants' information disclosure statement filed on 04/15/2005. The information referred to therein has been considered and a signed copy of the same is attached to this Office Action.

The Moyer Declaration & Applicants' Arguments

4) Acknowledgment is made of Applicants' submission of the Moyer Declaration filed 04/15/05 under 37 CFR 1.132, which has been fully considered.

The Moyer declaration describes the necessity of column-purified formulation in order to achieve the stability claimed in the instant application. The declaration asserts that column chromatography could be used to purify each botulinum toxin serotype claimed therein. The declaration acknowledges that Sacks as well as Ohishi taught the purification of a botulinum toxin using ammonium sulfate precipitation and ion-exchange chromatography. The Gartlan reference and the Schantz and Johnson reference are alleged as presenting work on non-column chromatographed botulinum toxin preparations. The 1971 Boroff reference is alleged as presenting work done on partially purified extracts of botulinum toxin preparations. Applicants submit that these cited articles are not relevant to the state of the prior art at the time of filing. The declaration further asserts that one of skill in the art at the time of filing would understand that the botulinum toxin serotypes were identical in functionality in connection with their

molecular target. The declaration describes that botulinum toxin serotypes A, B, C1, C2, D, E, F and G are similar in terms of physical characteristics as evidenced in the use of ammonium sulfate precipitation followed by column chromatography purification for each of the botulinum toxin serotypes. The declaration describes the nature of buffering agents and the guidance provided by the instant specification to allow one of ordinary skill in the art to use a pharmaceutically acceptable agent capable of buffering in the claimed ranges. Applicants cite several US patents and state that these patents teach the interchangeability of botulinum toxins in the treatment of a variety of neuromuscular diseases. Applicants state that they have provided extensive teaching regarding the purification of a wide range of the serotypes of botulinum toxin, and then preparing a formulation that is stable for extended periods of time. Applicants contend that purification of types A and B toxins are described in section III of the specification beginning at page 10, line 22, and that as stated at page 12, line 22 of the specification and in the Moyer declaration, botulinum toxin types C1, C2, D, E, F or G may be prepared and purified according to methods known in the art. Applicants conclude that one skilled in the art would understand how to adapt the disclosed methods to provide stable formulations comprising types A and C-G from reading the specification and references available prior to the filing of this application.

Applicants' arguments and the Moyer declaration have been carefully considered. The lack of scope of enablement rejection has been withdrawn upon further consideration. As recited currently, the botulinum toxin is not required to be column-purified. The statement in the declaration of the necessity for the botulinum toxin to column-purified formulation in order to achieve the stability claimed in the instant application has been particularly noted. In the 1970s, in addition to Sacks, column-purified botulinum toxin solutions were taught by others in the art to be stable in a buffer having a pH in the range of 5 and 6 $\pm$ 10%. See the teachings of Schwarz, 1979 below.

Prior Citation of Title 35 Sections

5) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

6) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Withdrawn

7) The rejection of claims 16, 17, 21 and 27 made in paragraph 9 of the Office Action mailed 06/01/04 under 35 U.S.C § 102(b) as being anticipated by *Schantz et al.* (*J. AOAC* 61: 96-99, 1978 - Applicants' IDS), is withdrawn in light of Applicants' amendments to the base claim.

8) The rejection of claims 1-28 made in paragraph 8 of the Office Action mailed 06/01/04 under 35 U.S.C. § 112, first paragraph, as being non-enabling with regard to the scope, is withdrawn upon further consideration.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

9) Claims 6, 7, 19 and 20 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 6 and 7 have improper antecedent basis in the limitation: 'said buffer'. Claims 6 and 7 depend directly or indirectly from claim 1, which does not recite a 'buffer', but a 'buffered saline'.

(b) Claims 19 and 20 have improper antecedent basis in the limitation: 'said buffer'. Claims 19 and 20 depend directly or indirectly from claim 16, which does not recite a 'buffer', but a 'buffered saline'.

Claim(s) Interpretation

10) The limitation 'purified' botulinum toxin in the instant claims is not limited to 'fully purified' botulinum toxin, but encompasses a botulinum toxin of any degree of purity. The fact that the botulinum toxin recited in the dependent claims 10 and 23 is required to be present as a 'complex' indicates that the 'purified' botulinum toxin recited in the base claims and claims dependent therefrom is not limited to fully purified botulinum toxin, but can be present in

association with a complex. The limitation 'purified botulinum toxin' in the base claims is not limited to column-purified botulinum toxin, but encompasses a botulinum toxin purified by any means. It is noted that the limitation 'liquid ... formulation' in the instant claims encompasses all liquid formulations that existed in the prior art before lyophilization and after reconstitution following lyophilization. The phrase 'said toxin formulation is stable .... degrees centigrade ...' is viewed as a functional limitation that does not define the formulation structurally. In the art rejections made below, the limitation 'said buffer' in the dependent claims 6, 7, 19 and 20 and the limitation 'buffered saline' in the independent claims 1 and 16 are viewed as having the same scope.

Rejection(s) under 35 U.S.C § 102

11) Claims 1-8 and 16-21 are rejected under 35 U.S.C § 102(b) as being anticipated by Schwarz (*Archiv. fur Lebensmittelhygiene* 30: 1-40, pp. 29-33, 1979 - original and translated documents, already of record).

The page number indicated below refer to the page number of the translated document.

Schwarz taught a stable liquid pharmaceutical formulation comprising a purified serotype B botulinum toxin and an acetate buffer solution having a pH in the range of 4.5 to 5.6, or a phosphate buffer at a pH of 6.0. The toxin was purified by ion exchange chromatography and was evaluated to be stable at 15°C. It is taught that at the pH range of 4.5 to 6.0, a greater stability can be established at a storage temperature of 15°C than at the higher pH values (see abstract; page 2; Figures 1-3 and 6-8; page 9; and page 10, last paragraph). A formulation comprising a purified type B botulinum toxin dissolved in a citrate-phosphate buffer of pH 5.6 is taught (see page 3). The toxin appears to be particularly stable at a pH value of 4.5. For a longer period, a solvent with a pH value under 6.0 is taught to be more suitable (see page 12). The prior art buffer having a pH in the range of 4.5 to 5.6 is expected to necessarily have a pK in the range of pH 4.5-6.5. Although Schwarz is silent about the functional limitation(s) on stability at the recited temperature or range of temperature for the recited period of time, these functional limitations are viewed as unrecited technical effects of Schwarz's stable liquid botulinum toxin pharmaceutical formulation which formulation was already known in the prior art. Since the

structural limitations are met by the prior art, the prior art stable pharmaceutical formulation is viewed as anticipating the instantly claimed product, which is expected to have the same functional properties as that of the Applicants' liquid formulation.

Claims 1-8 and 16-21 are anticipated by Schwarz.

12) Claims 1-8 and 16-21 are rejected under 35 U.S.C § 102(b) as being anticipated by Saprykina *et al.* (*Zh. Mikrobiol. Epidemiol. Immunobiol.* 9: 86-91, 1980).

Saprykina *et al.* disclosed a liquid botulinum type B toxin formulation comprising acid-precipitated toxin, which was subsequently extracted with citrate-phosphate buffer (i.e., pharmaceutically acceptable liquid buffered saline) with a pH of 5.6. See title and first paragraph on page 91. That the acid-precipitated and the buffer-extracted liquid botulinum toxin formulation of the prior art contains a botulinum type B toxin that is purified to some degree is inherent from the teachings of Saprykina *et al.* since acid-precipitation and buffer-extraction are expected to purify the toxin at least to some extent. The prior art buffer having a pH of 5.6 is expected to necessarily have a pK in the range of pH 4.5-6.5. Although Saprykina *et al.* are silent about the functional limitation(s) on stability at the recited temperature or range of temperature for the recited period of time, these functional limitations are viewed as unrecited technical effects of Saprykina's liquid botulinum toxin formulation which formulation was already known in the prior art. Since the structural limitations are met by the prior art, the prior art liquid formulation is viewed as anticipating the instantly claimed product, which is expected to have the same functional properties as that of the Applicants' liquid formulation.

Claims 1-8 and 16-21 are anticipated by Saprykina *et al.*

13) Claims 1-8 and 16-21 are rejected under 35 U.S.C § 102(b) as being anticipated by Sacks *et al.* (*Applied Microbiology* 28: 374-382, 1974 – Applicants' IDS).

Sacks *et al.* taught a stable preparation of a purified *Clostridium botulinum* type E toxin contained in a pH 6.0 phosphate buffer (see last incomplete paragraph on page 379). The toxin was column-purified (see third full paragraph on page 374, 376 and 379). Sacks *et al.* also taught a preparation of a purified *Clostridium botulinum* type E toxin contained in a pH 4.5 buffer which retained significant toxic activity (see pages 379 and 380) and therefore was stable. The prior art

buffer having a pH of 6.0 is expected to necessarily have a pK in the range of pH 4.5-6.5. Although Sacks *et al.* are silent about the functional limitation(s) on stability at the recited temperature or range of temperature for the recited period of time, these functional limitations are viewed as unrecited technical effects of Sacks' liquid botulinum toxin formulation which formulation was already known in the prior art. Since the structural limitations are met by the prior art, the prior art liquid formulation is viewed as anticipating the instantly claimed product, which is expected to have the same functional properties as that of the Applicants' liquid formulation.

Claims 1-8 and 16-21 are anticipated by Sacks *et al.*

14) Claims 1-8, 12-21 and 25-28 are rejected under 35 U.S.C § 102(b) as being anticipated by Schantz *et al.* (EP 0 593 176 A2, already of record) ('176).

Schantz *et al.* ('176) taught a pharmaceutical composition comprising 100 U of crystalline botulinum toxin type A toxin in a suitable buffer at a pH of about 5 to about pH 6.8 containing a stabilizing amount of a protein, such as, serum albumin (see page 2). Compositions comprising 100 or 1000 U of type A toxin in sodium citrate buffer with pH 5.0 or sodium phosphate buffer with 5.5 both containing the excipient protein, bovine serum albumin, are taught in Table 1. One particular toxin solution comprises sodium phosphate buffer of pH 6.2 and gelatin (see fourth full paragraph on page 3). Schantz *et al.* ('176) specifically taught that no detectable inactivation of type A crystalline toxin occurred during repeated freezing and thawing in sodium phosphate buffer having pH 6.2 to 6.8, sodium succinate buffer with pH 6.0 and sodium citrate buffer with pH 5.5 (see last paragraph on page 3). A pharmaceutical composition comprising a dissolved botulinum toxin in a buffer solution of pH 5.0 and a protein stabilizer such as serum albumin is taught (see claims 5-8). Schantz *et al.* ('176) taught that solutions of BSA or HAS have an unadjusted pH of 6.4 at which full recovery of the toxin activity takes place and that full recovery of toxin activity is obtained when the pH is adjusted to 5.0 or 5.5 (see page 4). The crystalline botulinum type A toxin was prepared by the same procedure used for the manufacture of the toxin in the current commercial product (see lines 18-19 on page 3) and therefore is viewed as inherently pure. The prior art buffer having a pH of 5.0, 5.5 or 6.2 is expected to necessarily have

a pK in the range of pH 4.5-6.5. Although Schantz *et al.* ('176) are silent about the functional limitation(s) on stability at the recited temperature or range of temperature for the recited period of time, these functional limitations are viewed as unrecited technical effects of Schantz's ('176) liquid botulinum toxin formulation which formulation was already known in the prior art. Since the structural limitations are met by the prior art, the prior art liquid formulation is viewed as anticipating the instantly claimed product, which is expected to have the same functional properties as that of the Applicants' liquid formulation.

Claims 1-8, 12-21 and 25-28 are anticipated by Schantz *et al.* ('176).

Rejection(s) under 35 U.S.C § 103

15) Claims 14, 15, 27 and 28 are rejected under 35 U.S.C § 103(a) as being unpatentable over Schwarz (*Archiv. fur Lebensmittelhygiene* 30: 1-40, pp. 29-33, 1979 - original and translated documents, already of record), or Saprykina *et al.* (*Zh. Mikrobiol. Epidemiol. Immunobiol.* 9: 86-91, 1980) or Sacks *et al.* (*Applied Microbiology* 28: 374-382, 1974 – Applicants' IDS) as applied to claim 1 or claim 16 and further in view of Schantz *et al.* (*Microbiol. Rev.* 56: 80-89, 1992) (Schantz *et al.*, 1992, already of record).

The teachings of Schwarz, Saprykina *et al.* or Sacks *et al.* are explained above which do not teach the presence of an excipient protein, such as, serum albumin, human serum albumin, or gelatin.

However, the use of an excipient protein, such as, bovine serum albumin, human serum albumin, or gelatin in a botulinum toxin liquid composition was well known in the art at the time of the invention in order to prevent the decrease in stability. For instance, Schantz *et al.* (1992) taught that the dilution of the purified botulinum toxin tends to decrease the stability of the neurotoxin, and that this decrease in stability can be prevented by diluting with a buffered solution containing a protein, such as gelatin, bovine serum albumin, or human serum albumin (see last paragraph on page 82). Schantz *et al.* (1992) taught that proteins such as gelatin and serum albumins are generally used to protect the botulinum toxin from detoxification occurring on diluting a solution of the botulinum toxin (see last full paragraph on page 83). Schantz *et al.* (1992) expressly taught that stabilization of the diluted botulinum toxin for longer periods

requires the presence of gelatin or serum albumin (see last full paragraph on page 81).

Given Schantz's (1992) express teaching that stabilization of the diluted botulinum toxin for longer periods requires the presence of gelatin or serum albumin, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add Schantz's (1992) gelatin or serum albumin to Saprykina's liquid formulation or Schwarz's or Sack's stable liquid formulation comprising the purified botulinum toxin to produce the instant invention with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of preventing the decrease in stability of the prior art liquid toxin formulation as taught by Schantz *et al.* (1992).

Claims 14, 15, 27 and 28 are *prima facie* obvious over the pror art of record.

16) Claims 9-11 and 22-24 are rejected under 35 U.S.C § 103(a) as being unpatentable over Schwarz (*Archiv. fur Lebensmittelhygiene* 30: 1-40, pp. 29-33, 1979 - original and translated documents, already of record), or Saprykina *et al.* (*Zh. Mikrobiol. Epidemiol. Immunobiol.* 9: 86-91, 1980) as applied to claim 8 or claim 21 above and further in view of Melling *et al.* (*Eye* 2: 16-23, 1988 – Applicants' IDS).

The teachings of Schwarz or Saprykina *et al.* are explained above which do not expressly disclose the concentration of the type B botulinum toxin to be in the range of 100-20,000 U/ml $\pm$ 10% or 1000-5000 U/ml.

However, adjusting the concentration of the type B botulinum toxin in an art-known liquid formulation to the desired concentration (U/ml) is well within the realm of routine experimentation.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to adjust or optimize the concentration of the type B botulinum toxin in Saprykina's liquid formulation or Schwarz's stable liquid pharmaceutical composition to a concentration that falls in the recited range of 100-20,000 U/ml $\pm$ 10% or 1000-5000 U/ml to produce the instant invention with a reasonable expectation of success. Adjustment of the concentration of a toxin in art-known liquid formulation is routine in the art, would have been well within the realm of routine experimentation, and would have been obvious to one of ordinary

skill in the art at the time of the instant invention. One of skill in the art would have been motivated to produce instant invention for the expected benefit of optimizing the concentration of the type B botulinum toxin in Saprykina's liquid formulation or Schwarz's stable liquid pharmaceutical composition. Since it is well known in the art that botulinum toxin is naturally co-produced and co-purified with a non-toxic protein with which the toxin is complexed as taught by Melling *et al.* (see last incomplete paragraph on page 16), the type B botulinum toxin in Saprykina's liquid formulation or Schwarz's stable liquid pharmaceutical composition is viewed as being present in a high molecular weight complex as recited in claims 10 and 23.

Claims 9-11 and 22-24 are *prima facie* obvious over the prior art of record.

17) Claims 12, 13, 25 and 26 are rejected under 35 U.S.C § 103(a) as being unpatentable over Sacks *et al.* (*Applied Microbiology* 28: 374-382, 1974 – Applicants' IDS) as applied to claim 8 or claim 21 above.

The teachings of Sacks *et al.* are explained above which do not expressly disclose the concentration of the type A botulinum toxin in their stable liquid preparation to be in the range of 20-2000 U/ml or 100-1000 U/ml.

However, adjusting the concentration of the type A botulinum toxin in an art-known stable formulation to the desired concentration (U/ml) is well within the realm of routine experimentation.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to adjust or optimize the concentration of the type A botulinum toxin in Sacks's stable liquid formulation to a concentration that falls in the recited range of 20-2000 U/ml or 100-1000 U/ml to produce the instant invention with a reasonable expectation of success. Adjustment or optimization of the concentration of a toxin in art-known stable liquid formulation is routine in the art, would have been well within the realm of routine experimentation, and would have been obvious to one of ordinary skill in the art at the time of the instant invention. One of skill in the art would have been motivated to produce instant invention for the expected benefit of optimizing the concentration of the type A botulinum toxin in Sacks' liquid formulation.

Claims 12, 13, 25 and 26 are *prima facie* obvious over the prior art of record.

Relevant Prior Art

18) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Halouzka *et al.* (*Folia Microbiol.* 37: 157-158, 1992 – Applicants' IDS) taught that botulinum toxin is resistant to the effect of extreme values of pH even at temperatures normally attainable in the mild climatic zone in summer (see page 158). Halouzka *et al.* taught that the toxin remained active over a broad pH range of 3.0 to 9.0 or a range of 2.7 to 10.2 despite the higher temperature of 28°C (see last paragraph on page 157).

Remarks

19) Claims 1-28 stand rejected.

20) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The central Fax number for submission of amendments, responses and papers is (571) 273-8300.

21) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

22) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's

supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

July, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER